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**13. ABSTRACT** ***(Maximum 200 Words)***

Our specific aims are to examine men with prostate cancer from 4 different racial-ethnic groups to determine the prevalence of molecular and cellular changes that may play a role in prostate tumor progression, particularly invasion and metastasis. We are currently assessing tissue samples from patients with prostate cancer for markers involved in the following pathways: a) hormonal regulation and responsiveness, b) cell cycle regulation c) tumor angiogenesis and its regulators and d) invasion and metastasis.

When our tissue analysis is completed we will determine the relationship between the changes in these key biological pathways and race/ethnicity, age and the intermediate markers of disease progression (i.e. tumor grade and stage).

Finally, these molecular and cellular changes will be related to clinical outcome (i.e survival and mortality) within and between racial/ethnic groups.

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Rene Cot 6/1/01

PI - Signature Date

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## INTRODUCTION

Prostate cancer continues to be a major health risk for men, and in fact, is the most frequently diagnosed cancer in the United States. Prostate cancer is remarkable for the extraordinary variation in incidence, mortality and survival among different racial-ethnic populations of men. African-American men have the highest rates of prostate cancer in the world and have substantially shorter survival times, even when analyzed on a stage by stage basis. Conversely, Asian men from China, Japan and Korea have the lowest rates of prostate cancer and appear to have substantially better survival times. Whites and Latinos have an intermediate incidence of disease occurrence and intermediate long-term survival times.

Although the epidemiology and etiology of prostate cancer is largely unknown and it is known to be a highly heterogenous disease with an unpredictable course, the steps that lead to tumor progression (i.e. invasion and metastases) are becoming increasingly well characterized. Among these are the following:

- Loss of hormonal regulation that can also have important implication s in the control of metastatic disease.
- Loss of cell cycle control: loss of tumor suppressor function (e.g. p53, Rb, PTEN) that can have multiple effects on regulation of cell growth, angiogenesis, and the ability of a tumor to enter the cell death (apoptotic) pathway. Similarly, inactivation of cdk-inhibitors (p27,p21,p16) is expected to result in increased proliferation rates of tumor cells (as detected by PCNA, Ki67 and Topoisomerase II expression).
- Loss of growth control: in the past few years, a number of groups have identified loss of function of the PTEN phosphatase as a common event, particularly in advanced prostate cancer. The primary consequence of loss of PTEN function is deregulation of the PI3-kinase Akt pathway, which is oncogenic in many tumor models. By measuring the status if this pathway at multiple levels, we will be defining the frequency of this change in multiple ethnic groups.
- The ability to form a new blood supply (angiogenesis) a factor vital for the transport of nutrients and removal of wastes from a tumor as well as providing a route for tumor metastasis. Loss of normal inhibitors of angiogenesis (thrombospondin-1) can lead to increased neovascularization (detected by microvascular density).
- Loss of normal cell matrix adhesion properties and cell-cell interactions (including contact inhibition), that allows tumor cells to grow past normal cell density and to break away from their primary site and form occult metastases, or overt metastases.

We are in the process of determining the relationship between changes in these key biological pathways and a) race/ethnicity, b) age, and c) intermediate markers of tumor progression (tumor stage and grade). We will eventually be in a position to relate these changes to the overall and disease-free rates, across racial-ethnic groups.

BODY

We are in the process of testing our hypothesis that the difference in tumor behavior among the different racial-ethic groups as a molecular and cellular basis. We have been collecting specimens from the CSP Slide Retrieval Resource, a component of the Tissue Procurement Core Resource of the USC/Norris Comprehensive Cancer Center. This core resource handles all requests to hospitals and freestanding pathology laboratories for tumor tissue. In addition, we have been able to obtain tissue using the SEER registry in Los Angeles County, a highly multiethnic population. We have collected over 161 tumor samples from patients with prostate carcinoma. Initial delays in collecting these samples were encountered due to difficulty in procuring the tissues from the participating institutions. However, as stated we have over 161 samples and continue to collect samples. The registry maintains the main patient database and provides us with glass slides from patients with prostate cancer, stripped of patient names. During our analysis of the tissues, we are blinded to the clinical stage and grade of the tumor as well as to the patient's race. The Department of Preventative Medicine headed by our Co-investigator, Dr. Ronald Ross, maintains a complete database concerning the relevant clinical and demographic information regarding the patient as well as the links to the patient identification from all cohorts of patient samples being examined. We receive the specimens from the Department of Preventative Medicine, labeled with a pathology number and a study number. We enter these data into our laboratory database a give them laboratory numbers. The results are transmitted back to the Department of Preventative Medicine for statistical analysis. We assess all the tumor tissue obtained to ensure uniform pathologic tumor grading and to evaluate the suitability for its use in this project. These tumor samples are in the process of being analyzed for various factors that are thought to play a role in tumor progression. These factors include p27, bcl-2, E-cadherin, p53, Rb, CD34, p16, Ki67, PCNA, Topoisomerase-II and thrombospondin-1.

Since beginning this project new and exciting data regarding Cyclooxygenase-2 (COX-2), a carcinogen-activating (Phase 1) enzyme thought to exhibit an inhibitory effect on apoptosis, activity and tumor progression in cancer has been reported. Three recent, relatively small and non-population based studies of bladder cancer have demonstrated expression of COX-2. In the first study, COX-2 expression was detected in 25/29 (86%) invasive transitional cell carcinomas of the urinary bladder and in 6/8 (75%) casescarcinoma *in situ* [1]. In the second study, 12/16 transitional cell carcinoma specimens wee COX-2 positive compared with 2/8 'normal' adjacent tissues (p=0.03) [2]. Finally, Liebert et al [3] showed that while low-stage bladder cancers were generally negative for COX-2 (4/14 Ta/T1/TIS expressed COX-2), most invasive tumors (10/12) expressed COX-2. In light of these exciting preliminary data regarding COX-2 and its potential role in the pathogenesis of cancer [4, 5], we have added this to our list of markers to study in prostate cancer.

Due to the limited amounts of tumor we receive, not all markers can be performed on all tumors. Due to an unforeseen turnover in laboratory technical staff, there was a delay in the initial processing of these specimens. We now have 2 new full-time technicians who are now fully-trained to process these specimens. For these reasons we have been

granted a 1-year, no cost extension. We fully expect to have reached our objectives, with the exception of the long-term recurrence and survival outcomes by April 2002.

These studies are expected to provide information leading to better understanding of prostate cancer progression in men of different racial-ethnic groups. Preliminary results show differences p27 expression from tumor to tumor, however, the results are still blinded and no conclusions can yet be stated.

While our project will have emphasis on racial-ethnic variability, it will also address important issues concerning prostate cancer outcome for all men. Facts that predispose one group of men to have more aggressive tumor, may be predictive of behavior of prostate cancer in all men.

KEY RESEARCH ACCOMPLISHMENTS

- Accrual of more 161 prostate cancer samples
- Pathologic evaluation of tumor samples, including Gleason Grading, percent tumor and suitability of us in project
- Access database created for all tumor evaluation and marker results
- IHC on suitable tumor samples
- Assessment of markers by pathologist (DH)

REPORTABLE OUTCOMES

This project has served as the springboard for another project that has been funded by the DOD (DAMD-17-00-1-0102) led by Dr. Ronald Ross in which the SEER cohort of patients has been added as well as two new projects involving androgen receptor signaling in prostate cancer lead by Dr. G Coetzee and Dr. J Reinhardt. This new award has benefited this study by introducing a new cohort of patients without further costs to this project. Furthermore, this work has lead to the recent (June 1, 2001) submission of a SPORE Grant on Prostate cancer to the NIH.

A visiting research fellow Dr Weiguang Mo, a fully trained Pathologist from China will be joining the laboratory for one year to work on this project (see attached CV in appendix).

CONCLUSIONS

This study is a molecular epidemiologic study designed to elucidate the factors involved in disease progression. Our data will elucidate differences in prostate cancer risk and progression across multi-ethnic lines (African-American, Asian, Latino and white) including understudied populations of men. We have and are continuing to develop and apply novel biologic markers of prostate cancer progression.

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# CURRICULUM VITAE


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Selected Publications:


1. Mo WG, et al. Experimental ultrastructure study on kidney injury due to star-fruits. Chinese J Physical Med. 19(3):186, 1997
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REPLY TO
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